Pten null prostate tumorigenesis and AKT activation are blocked by targeted knockout of ER chaperone GRP78/BiP in prostate epithelium.

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Public Summary:
Prostate cancer is the most common cancer in men and tumor often develops resistance and relapse after surgery or treatment. Thus it is critical to identify novel candidates to target prostate cancer. Glucose-regulated protein, 78 kDa, GRP78, is a key chaperone in the endoplasmic reticulum (ER) that maintains ER homeostasis. High GRP78 expression is associated with poor prognosis in prostate cancer, but its role and mechanism are unknown. By genetically deleting GRP78 in mice prostate epithelium, prostate tumorigenesis was suppressed, as well as the activation of key oncogenic signaling. This study described a previously unidentified approach to suppress prostate cancer development.

Scientific Abstract:
GRP78/BiP has recently emerged as a novel biomarker for aggressive prostate cancer. Here, we report that homozygous deletion of Grp78 specifically in mouse prostate epithelium suppresses prostate tumorigenesis without affecting postnatal prostate development and growth. Mouse prostates with double conditional knockout of Grp78 and Pten exhibit normal histology and cytology, in contrast to the invasive adenocarcinoma in mouse prostates with Pten inactivation. AKT activation in Pten null prostate epithelium is inhibited by Grp78 homozygous deletion, corresponding with suppression of AKT phosphorylation by GRP78 knockdown in prostate cancer cell line. Thus, inactivation of GRP78 may represent a previously undescribed approach to stop prostate cancer and potentially other cancers resulting from the loss of PTEN tumor suppression and/or activation of the oncogenic AKT.

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